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⑷ Process for determination of a complete or a partial contents of very short sequences in the samples of nucleic acids connected to the discrete particles of microscopic size by hybridization with oligonucleotide probes.

⑷ Determination of the formula of genomic DNA, i.e. genome sequencing, by a hybridization with oligonucleotide probes (YU Patent Application 570/87) envisages the use of 100000 oligonucleotide probes and the same number of hybridizations with 6000000 of addressed sample-clones on filters in order to determine contents of oligonucleotide sequences in each clone. The process presents improvements in preparation of samples for hybridization and improvements which enable one to follow gene expression by determining partial or complete fragment sequences of genomic DNA, mRNA or cDNA. By binding fragments of genomic DNA to discrete particles (DP) of a microscopic size which are recognizable in a step of reading experimental image, the necessity for addressed samples on filters is dispensed with and this drastically reduces automatical-robotical component of the process and allows miniaturization of the entire method from a level of industrial installation to the level of laboratory instrument. Processes for binding DNA fragments to DPs recognizable in common reactions, allow elimination of cloning, i.e. DNA amplification in the host

cells and, in a process of library forming, need for formation of 6000000 addressed samples in any one of the phases of a process for sequencing by hybridization.

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REPORT

Application Number

EP 90 10 7066

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	GENOMICS, vol. 4, no. 2, February 1989, pages 114-128, Academic Press, Inc.; R. DRMANAC et al.: "Sequencing of megabase plus DNA by hybridization: Theory of the method" * The whole document; esp. abstract; page 115, column 1, lines 33-48; page 120, column 1, line 30 - column 2, line 27 *	1,14	C 12 Q 1/68
Y	WO-A-8 603 782 (A. MALCOLM et al.) * Page 3, line 7 - page 4, line 23; claims 1,2 *	1,14	
A	CHEMICAL ABSTRACTS, vol. 110, no. 17, 24th April 1989, page 229, abstract no. 149154a, Columbus, Ohio, US; Y.P. LYSOV et al.: "Determination of the DNA nucleotide sequence by hybridization with oligonucleotides. A new method", & DOKL. AKAD. NAUK SSSR 1988, 303(6), 1508-1511 * Abstract *	1,14	
A	JOURNAL OF THEORETICAL BIOLOGY, vol. 135, no. 3, 7th December 1988, pages 303-307, Academic Press, London, GB; W. BAINS et al.: "A novel method for nucleic acid sequence determination" * The whole document, esp. abstract; page 306, lines 1-31 *	1	
A	CELL, vol. 50, 31st July 1987, pages 495-508, Cell Press; Y. KOHARA et al.: "The physical map of the whole E. coli chromosome: Application of a new strategy for rapid analysis and sorting of a large genomic library" * Abstract; page 496, column 2, lines 1-12; figure 4; page 499, column 1, line 25 - column 2, line 52; page 504, column 1, line 31 - page 505, column 2, line 51 *	1	C 12 Q

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	07 June 91	LUZZATTO E.R.P.G.A.
<b>CATEGORY OF CITED DOCUMENTS</b>		
X: particularly relevant if taken alone		E: earlier patent document, but published on, or after the filing date
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A: technological background		L: document cited for other reasons
O: non-written disclosure		
P: intermediate document		
T: theory or principle underlying the invention		&: member of the same patent family, corresponding document

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EP 90 10 7066

## DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,Y	FEBS LETTERS, vol. 256, nos. 1,2, October 1989, pages 118-122, Elsevier Science Publishers B.V. (Biomedical Division); K.R. KHRAPKO et al.: "An oligonucleotide hybridization approach to DNA sequencing" * The whole document *	1,14	
E	WO-A-9 004 652 (DNAX RESEARCH INSTITUTE) * The whole document, especially page 3, lines 3-27; page 5, lines 17-27; page 10, lines 20-31; page 20, lines 8-12; claims 1,3 *	1	
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	
The Hague		Examiner	
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention		E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document	